Article

Not peer-reviewed version

Neurocognitive Changes in Patients with Post-COVID Depression

Marina Khodanovich *, Anna Naumova, Daria Kamaeva, Victoria Obukhovskaya, Svetlana Vasilieva, Evgeny Schastnyy, Nadezhda Kataeva, Anastasia Levina, Marina Kudabaeva, Valentina Pashkevich, Marina Moshkina, Yana Tumentceva, Mikhail Svetlik

Posted Date: 13 December 2023

doi: 10.20944/preprints202312.0937.v1

Keywords: COVID-19; post-COVD; long COVID; depression; major depressive disorder; cognitive impairment; MoCA; Word Memory Test; Stroop Color Word Test; Trail Making Test; Insomnia Severity Index

Article

Neurocognitive Changes in Patients with Post-COVID Depression

Marina Khodanovich [1,*], Anna V. Naumova [1,2], Daria Kamaeva [3], Victoria Obukhovskaya [1,4], Svetlana Vasilieva [3], Evgeny Schastnyy [3], Nadezhda Kataeva [1,4], Anastasia Levina [1,5], Marina Kudabaeva [1], Valentina Pashkevich [1], Marina Moshkina [1], Yana Tumentceva [1] and Mikhail Svetlik [1].

[1] Laboratory of Neurobiology, Research Institute of Biology and Biophysics, Tomsk State University, 36 Lenina Ave., Tomsk 634050, Russia; khodanovich@mail.tsu.ru
[2] University of Washington, Seattle, WA, United States; 850 Republican Street, Seattle, WA 98109, United States; nav@uw.edu
[3] Mental Health Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk, 634014, Russia; susl2008@yandex.ru
[4] Siberian State Medical University, 2 Moskovskiy Trakt, Tomsk, 6340505, Russia; diada1991@gmail.com
[5] Medica Diagnostic and Treatment Center, 86 Sovetskaya st., Tomsk, 634510, Russia; nastasio@yandex.ru
* Correspondence: khodanovich@mail.tsu.ru

Abstract: Depression and cognitive impairment are recognized complications of COVID-19. This study aimed to assess cognitive performance in clinically diagnosed post-COVID depression (PCD) patients using neuropsychological testing. The study involved 71 post-COVID patients, with matched control groups: recovered COVID-19 individuals without complications (n=18) and individuals without prior COVID-19 history (n=19). A post-COVID depression group (PCD, n=25) was identified based on psychiatric diagnosis, a comparison group (noPCD, n=46) included participants with neurological COVID-19 complications, excluding clinical depression. The PCD patients showed significantly less scores in the MoCA test, decreased immediate memory recall in the Word Memory Test, decreased processing speed and higher accuracy in the Trail Making Test, and near to significant worse executive control and processing speed in the Stroop task compared to controls and the noPCD patients. The number of post-COVID symptoms negatively correlated with immediate word memory recall and processing speed among all post-COVID patients. In PCD patients, negative correlations between number of post-COVID symptoms and delayed recall, between time after recovery and immediate recall, and positive correlation between the number of acute symptoms and processing speed in the incongruent condition of the Stroop task were found. No differences between groups in Sniffin's stick olfactory test was found. Overall, our study revealed cognitive impairment in PCD patients similar to those in major depressive disorder.

Keywords: COVID-19; post-COVD; long COVID; depression; major depressive disorder; cognitive impairment; MoCA; Word Memory Test; Stroop Color Word Test; Trail Making Test; Insomnia Severity Index

1. Introduction

Post-COVID syndrome is defined as a state following COVID-19 in people with a probable or confirmed history of infection, usually occurring 3 months after the onset of COVID-19 symptoms and lasting at least 2 months, and which cannot be explained by an alternative diagnosis [1]. In September 2020, WHO introduced the corresponding codes denoting the post-COVID-19 condition, including post-Covid syndrome, International Classification of Diseases (ICD)-10 code (U09) and ICD-11 code (RA02).

To date, a large amount of evidence regarding cognitive and depressive impairments in the post-COVID patients has accumulated [2–11]. SARS-CoV-2 infection is associated with an increased risk of developing mental disorders, including depression, which are detected both during the acute

 doi:10.20944/preprints202312.0937.v1

phase and in the post-COVID period. A study by Ma at al [12] reported that 43.1% of patients showed signs of depression based on data from the online self-questionnaire 9-item Patient Health Questionnaire (PHQ-9) during the acute period of coronavirus infection. A retrospective cohort study by Taquet M. et al., 2021, including 236,379 patients, demonstrated that mood disorders, anxiety and psychotic disorders as consequences of COVID-19 were detected in 23.98% of people who had the infection [3].

A significant proportion of post-COVID patients report depressive symptoms as well as cognitive impairment [2–13]. These changes are similar to the cognitive changes seen in major depressive disorder (MDD) [14–17]. Cognitive impairment in patients with MDD is manifested by deficits in executive function, processing speed, memory, and attention [14–17]. Several factors influence cognitive decline in MDD such as age, age at onset of depression, level of education, MDD subtype, inflammatory status, treatment regimen, and childhood adversity [16]. The relationship between post-COVID depression and cognitive impairment and the impact of the factors above, is poorly understood. Despite the large number of published studies, most of them are based on survey results for depression that are not confirmed by a psychiatrist's diagnosis. It is still unclear whether post-COVID depression (PCD) and cognitive impairment in post-COVID depression have specific features different from MDD.

In the published studies on post-COVID patients, data on cognitive impairment and depressive symptoms were mainly obtained through self-assessment questionnaires [4,7,8,11,18–20]. Few studies used standardized tests for this assessment [5,9,10]. Since self-reported symptoms and performance on cognitive tests may differ significantly [21]. The standard psychometric tests might characterize the features of post-COVID cognitive impairment, including patients with clinical depression, more precisely and objectively. The use of standard tests will also help to more clearly define the general and specific features of PCD in comparison with MDD.

The present study aimed to evaluate cognitive function in patients with clinically diagnosed post-COVID depression (PCD) using objective neuropsychological testing and associations between COVID-19 parameters and cognitive impairment in PCD depression.

2. Materials and Methods

2.1. Study participants and clinical assessment

The study participants (n=109) were recruited by Mental Health Research Institute (Tomsk, Russia), Medica Diagnostic and Treatment Center (Tomsk, Russia), and Tomsk State University (Tomsk, Russia) between September 2022 and June 2023. The inclusion criteria were the following: age from 18 to 61 years, the absence of the history of traumatic brain injury, and the absence of any diagnosed neurologic or psychiatric condition prior to COVID-19. The exclusion criteria were: previous positivity to COVID-19 (except for the control group), contraindications to MRI, inability to tolerate the MRI procedure, and self-withdrawal from the study. Written informed consent was obtained from all participants. The study design was approved by the local Ethical Committee of the Mental Health Research Institute (protocol №15/8.2022) and Bioethics Committee of Tomsk State University (№12/06.2022) following the guidelines of the Declaration of Helsinki.

The Hospital Anxiety and Depression Scale (HADS) [22] was used to screen for symptoms of anxiety and depression. All subjects were assessed by a clinical psychologist, and those who scored higher (>8) on the HADS were assessed by a psychiatrist. A group of patients with affective disorder was formed by a psychiatrist based on a structured clinical interview for ICD-10 and baseline assessment report, including socio-demographic characteristics, medical history, questionnaire regarding COVID-19, clinical and psychometric examination. The severity of the current depressive episode was assessed before the start of drug therapy using the Hamilton Rating Scale for Depression (HDRS) [23,24]. The total score is interpreted as follows: no depression (0-7); mild depression (8-16); moderate depression (17-23); and severe depression (≥24).

The individuals (n=25) with diagnosed clinical depression (moderate depressive episode - F32.1, severe depressive episode without psychotic symptoms – F32.2, recurrent depressive disorder (first

 doi:10.20944/preprints202312.0937.v1

diagnosed at the time of the study), current episode moderate – F33.1, according to ICD-10) were included in the post-COVID depression (PCD) group. The participants (n=46) with neurological complications of COVID-19 and without clinical depression were included in the comparison group (noPCD group). The first control group (n=19) included healthy volunteers who were not COVID-19 positive and did not experience symptoms of COVID-19 from the start of the pandemic until the time of examination. The second control group (ControlPC, n=18) was formed from volunteers who had suffered COVID-19 but did not experience post-COVID symptoms at the time of the research. The demographic characteristics of participants are shown in Table 1. The groups did not differ significantly in age, gender, education, and severity of COVID-19 (PCD and noPCD groups) according to Chi-square criteria.

Table 1. The demographic characteristics of participants of the study.

Parameter	PCD	NoPCD	ControlPC	Control
Sample size	25	46	18	19
Male (%)	4(16)	17(37)	7(39)	8(42)
Female (%)	21(84)	29(63)	11(61)	11(58)
Education, years±SD	15.2±1.9	15.9±2.1	16.1±2.4	16.4±1.8
Age, years±SD	37±13.7	43±10.4	43.7±9.7	38.3±10.3
Age, median (min-max)	42.0(19-59)	43(21-61)	42(24-61)	39(20-58)

2.2. Questionnaire to assess acute and post-COVID symptoms

All participants except for the control group filled out a COVID-19 questionnaire. The questionnaire included questions about the number, severity, and date of illnesses, the PCR tests, vaccination, symptoms of the acute and post-COVID phases. As symptoms of the acute phase, patients were asked to note the presence or absence of anosmia, ageusia, fever, difficulty breathing, cough, muscle weakness, myalgia, headache, and dizziness. As symptoms of the post-COVID phase, patients were asked to note the presence or absence of headache, dizziness, brain fog, anosmia, ageusia, sensitivity, hypertensia/hypotensia, insomnia, fatigue, attention and memory deficit, myalgia, depression, panic attacks. Based on the results of the answers, the number of symptoms in the acute and post-COVID phases was calculated as the sum of symptoms (1 symptom – 1 point), for which positive answers were given for all diseases. The number of symptoms has proven itself well as an independent predictor of post-COVID complications and for assessing the severity of post-COVID [25–28].

2.3. Neuropsychological assessment

All participants were evaluated with the several psychometric tests. The procedure was carried out by a clinical psychologist. The psychometric testing included the Montreal Cognitive Assessment (MoCA) [29], the Word Memory Test (WMT) [30,31], Trail Making Test, (TMT) [32], Stroop Color Word Test (SCWT) [33,34], olfactory test, and the Insomnia Severity Index questionnaire.

2.3.1. Montreal Cognitive Assessment (MoCA)

The Russian version [35] of the Montreal Cognitive Assessment (MoCA) test [29], version 7.1 [36], is used for global assessment of cognitive function. Within the MoCA test (30 points maximum) 7 indexes [36] evaluated visuospatial/executive abilities (0-5 points), naming (0-3 points), attention (0-6 points including forward and backward digit span (0-2), vigilance (0-1) calculation (0-3 points), language (0-3 points), abstraction (0-2 points), short-term memory (0-5 points), orientation to time and place (6 points). A total score of 25 and more was classified as normal, while 25 or less as cognitive impairment [29,35].

2.3.1. Olfactory testing

 doi:10.20944/preprints202312.0937.v1

Olfactory testing was performed with Sniffin' Sticks Test kit (ODOFIN, France) [37,38]. The subject sequentially identified 12 smells from a standardized set of well-known odors (coffee, orange, garlic, cloves, etc.), making a choice from 4 proposed options. The identification version of the test was used. The odor was presented for 3 seconds, the pause between the presentation of odors was 30 seconds. The number of correct answers was counted.

2.3.1. Stroop Color Word Test

Cognitive control was measured using the Russian version of the classical Stroop task [33,34] as modified by Cousijn et al. [39]. The test consisted of three subtests. The material for each subtest was one sheet of white paper on which 100 words or single-color hexes were printed in random order. In the first subtest (word condition, W), the words were printed in black ink and meant four colors: "синий" (blue), "зеленый" (green), "красный" (red), "желтый" (yellow). Participants had to read the words out loud as quickly as possible. In the second subtest (color condition, C), participants saw solid-color hexes (blue, green, red, or yellow) and were asked to name the color. In the third subtest (word-color condition, WC), the printed words were related to the same four colors but were printed in a mismatched color (e.g., the word "blue" printed in red ink) and in matched colors. The total time in seconds spent completing each of the three subtests was measured. Additionally, an interference effect was calculating the ratio between the times required for the W and C conditions (low interference), and the ratio between the times required for the CW and C conditions (high interference) [40].

2.3.3. Word Memory Test

In the Word Memory Test (WMT) [30,31] 10 printed unrelated words were presented to participant. The participant was instructed to read and remember each word. After the presentation of words, immediate recall was assessed. If the participant did not reproduce all the words, the psychologist tried to help him by associations to the missing word (assistance). About 15 minutes later the participant was asked to reproduce the previously memorized words. After this, the psychologist tried to recall the missing words using associations. Scores were assigned for immediately reproduced words (0-10 points), delayed words reproduced (0-10 points), and words, additionally reproduced with the assistance of a psychologist.

2.3.3. Trail Making Test

The Trail Making Test (TMT), part A [32], was used to assess the speed of information processing. The participant was asked to connect 25 numbered circles in sequence (Part A). The time spent on the task and the number of errors were recorded.

2.3.1. Insomnia Severity Index

The Insomnia Severity Index (ISI) [41] was used to identify the nature, severity and impact of insomnia on daily life over the past two weeks. This self-report questionnaire rates from 0 to 4 each of parameters: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. The total score is interpreted as follows: no insomnia (0-7); mild insomnia (8-14); moderate insomnia (15-21); and severe insomnia (22-28).

2.5. Statistical analysis

Statistical analysis was performed using Statistica 10.0 software. Differences between groups were analyzed using the one-way analysis of variance (ANOVA) followed by post-hoc Fisher LSD tests. Differences in symptom frequencies between groups were analyzed using the Chi-square test. Associations between COVID-related parametric variables (number of COVID-19 episodes, time after the first and last COVID-19, number of acute and post-COVID symptoms) and the results of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 December 2023 doi:10.20944/preprints202312.0937.v1

psychometric tests were assessed using the Pearson correlation coefficient. Comparisons were considered statistically significant for all analyzes was taken with p less than 0.05.

3. Results

3.1. Clinical assessment of the patients with post-COVID depression

The patients developed a depressive episode following a COVID-19 infection were combined into the post-COVID depression (PCD) group. Among 25 patients with PCD, 44% showed symptoms of atypical depression, such as increased appetite, weight gain, sleeping more than 10 hours, emotional reactivity, heaviness in the limbs, or chronic fatigue. Suicidal tendencies were identified in 52% of patients. Clinical characteristics of patients with PCD are presented in table 2.

Table 2. Clinical characteristics of the patients with PCD (n=25).

Parameter	mean±SD
Hamilton score (HDRS)	18.36±3.66
Age of manifestation, years	34.62±13.96
Number of episodes	1.75±1.75
Duration of last episode, month	8.27±7.31

3.1. Acute and post-COVID symptoms

Group characteristics related to disease severity, time since first and last COVID-19, symptoms in the acute and post-COVID phases are presented in Table 3.

Table 3. The severity of COVID-19, acute and post-COVID symptoms of participants of the study.

Parameter	PCD	noPCD	ControlPC	Statistics
Severity, mild/moderate/severe/critical (%)	88/8/4/0	63/17/15/4	66/28/0/1	
Number of COVID-19 episodes, mean±SD	1.60±0.71	1.65±0.77	1.50±0.51	F(2, 86)=0.30, p=0.74
Time after the first COVID-19, months±SD	20.3±8.2	21.8± 9.4	16.3±6.4	F(2, 86)=2.6, p=.08
Time after last COVID-19, months±SD	13.1±10.3	15.0±10.5	9.8±5.5	F(2, 86)=1.8, p=0.16
Acute symptoms				
Anosmia, n (%)	22(88%)	34(74%)	15(83%)	-
Ageusia, n (%)	19(76%)*	27(59%)	8(44%)	-
Fever, n (%)	22(88%)	44(96%)	16(89%)	-
Difficulty breathing, n (%)	14(56%)	27(59%)	7(39%)	-
Cough, n (%)	22(88%)	32(70%)	13(72%)	-
Muscle weakness, n (%)	24(96%)	42(91%)	15(83%)	-
Myalgia, n (%)	20(80%)	30(65%)	10(56%)	-
Headache, n (%)	22(88%)*	34(74%)	11(61%)	-
Dizziness, n (%)	14(56%)	28(61%)*	6(33%)	-
Number of acute symptoms	7.24± 1.85*	6.48±2.21	5.61±1.94	F(2, 86)=3.28, p=0.042
Post-COVID symptoms				
Headache, n (%)	7 (28%)	6(13%)	2(11%)	-
Dizziness, n (%)	10 (40%)#	22(48%)##	2(11%)	-
Brain fog, n (%)	14 (56%)	19(41%)	6(33%)	-
Anosmia, n (%)	16 (64%)*&	16(35%)	5(28%)	-
Ageusia, n (%)	14 (56%)**&	12(26%)	3(17%)	-
Sensitivity, n (%)	3 (12%)	7(15%)	1(6%)	-
Hypertensia/hypotensia, n (%)	7 (28%)	23(50%)*	4(22%)	-
Insomnia, n (%)	20 (80%)***	27(59%)***	5(28%)	-
Fatigue, n (%)	24(96%)***&	36(78%)**	8(44%)	-
Attention deficit, n (%)	23(92%)***&&	29(63%)***	4(22%)	-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 December 2023 doi:10.20944/preprints202312.0937.v1

Memory deficit,%	19(76%)***	39(85%)	4(22%)	-
Mialgia, n (%)	15(60%)*	25(54%)	5(28%)	-
Depression, n (%)	24(96%)***&&&	24(52%)**	2(11%)	-
Panic attacks, n (%)	5(20%)*	3(7%)	0(0%)	-
Number of post-COVID symptoms	8.04±2.23*** &	6.26±2.95***	2.83±3.24	F(2, 86)=17.95, p=0.000

Data are presented as mean±SD. Significant differences relative the ControlPC group: * - p<0.05, ** - p<0.01, *** - p<0.001. Significant differences between the PCD and noPCD groups: & - p<0.05, && - p<0.01, &&& - p<0.001.

Symptoms in PCD patients differed significantly from the ControlPC and noPCD group in both the acute phase of the disease and the post-COVID phase. In the acute phase, the number of symptoms in the PCD group was significantly higher than in other studied groups. Ageusia and headache were checked more often in the questionnaire in comparison with the ControlPC group. However, these differences between groups were borderline statistically significant. The patients from the noPCD group more often felt dizziness than the ControlPC group. The total number of acute symptoms in the noPCD group in the acute phase was also higher compared to the ControlPC group while no difference between the PCD and noPCD groups were obtained.

In the post-COVID phase, the differences in symptoms between the studied groups were more essential. In the PCD group, more than half of the patients experienced anosmia and ageusia (64% and 56% correspondingly, p<0.05 vs the ControlPC group), while in the noPCD group only 29% and 21% reported these symptoms. Almost all patients in the PCD group reported sleep disturbances, fatigue, attention deficits, and depression. In contrast, half or fewer patients in noPCD group reported these symptoms (p<0.05 between groups for fatigue, attention deficit and self-estimated depression). Both the PCD and noPCD groups differ significantly from the ControlPC group in insomnia, fatigue, and depression. The PCD patients also had the symptoms of memory deficit, myalgia, and panic attacks more often than control. The average number of symptoms of patients in the PCD group was 1.3 times higher than in the noPCD group and 2.8 times higher than in the ControlPC group.

3.2. Results of neuropsychological testing

Patients in the PCD group showed significantly higher scores on the HARS depression-related scales, both compared with both control groups and the noPCD group (Table 4). In addition, patients in the PCD group show a significantly higher insomnia when compared to controls as well as to the noPCD group.

In the MoCA cognitive test, all indexes for the PCD and noPCD group were lower than in both control groups. The difference was statistically significant in assessment of the total score (p<0.05). Only 16% of patients with PCD and 15% of noPCD patients had a marked decline in cognitive function with total score less than 25 points.

In the Word Memory test (WMT), both the PCD and noPCD groups showed significantly worse immediate word recall and total score in comparison with both control groups. However, the immediate word recall in the PCD patients was significantly worse than the patients of the noPCD group.

The Trail Making Test (TMT) showed longer processing time of test performance for PCD and noPCD patients compared to both control groups. However, the number of errors in this test for patients with depression was significantly less than in controls.

The Stroop Color Word Test (SCWT) did not show significant intergroup differences although the PCD group tended to show longer processing in the simple congruent W condition, as well as a worse interference index for more comprehensive task, compared with controls.

No differences between groups were found in the olfactory testing.

Table 4. The results of neuropsychological testing.

Test	Parameter	PCD	noPCD	ControlPC	Control
HADS	Total score	21.04±7.40 *** ### &&&	10.91±5.69 * &&&	8.38±3.90	7.89±3.75

 doi:10.20944/preprints202312.0937.v1

	Anxiety	10.84±3.25 *** ### &&&	6.19±3.68 * &&&	4.78±3.09	4.42±2.41
	Depression	10.36±4.78 *** ### &&&	4.93±3.22 &&&	3.50±2.90	3.47±2.44
ISI	Total score	14.56±7.02 *** ### &&&	9.11±6.17 ### &&	4.11±3.79	6.11±4.62
MoCA	Total score	26.48±2.10 *	26.59±2.16 *	27.78±1.99	27.63±1.54
	Visuospatial/executive abilities	4.28±0.89	4.48±0.75	4.61±0.98	4.58±0.69
	Naming	3.0±0.0	3.0±0.0	3.0±0.0	3.0±0.0
	Attention	5.44±0.77	5.37±0.95	5.89±0.32	5.84±0.37
	Language	2.32±0.63	2.11±0.95	2.39±0.70	2.32±0.75
	Abstraction	1.96±0.20	1.93±0.25	2.0±0.0	1.95±0.23
	Memory	3.56±1.36	3.76±1.30	4.00±1.14	4.05±1.03
	Orientation	5.92±0.28	5.93±0.25	5.89±0.32	5.89±0.32
WMT	Total score	18.12±2.71* # &	18.98±1.34 &	19.44±0.92	19.10±1.17
	Immediate recall	7.08±1.58 **	7.65±1.29*	7.83±1.54	8.42±1.35
	Immediate assistance	1.96±1.06**	2.09±1.28*	2.11±1.49	1.47±1.17
	Immediate total	9.04±1.40 *** ### &&&	9.70±0.51 &&&	9.94±0.24	9.83±0.48
	Delayed	6.83±2.01	6.72±1.93	7.22±1.83	7.34±1.95
	Delayed assistance	2.12±1.30	2.52±1.56	2.22±1.44	1.73±1.69
	Delayed total	9.04±1.65	9.26±1.02	9.50±0.86	9.21±1.18
SCWT	W, time (s)	55.40±12.22 (p=0.05 vs Control)	51.76±7.07	55.67±12.50	49.68±7.82
	C, time (s)	68.80±21.74	68.91±12.99	67.11±13.03	65.16±19.99
	CW, time (s)	119.12±35.46	121.33±23.23	116.83±31.48	110.32±38.90
	Low interference	1.05±1.28	0.77±0.14	0.83±0.11	0.80±0.16
	High interference	2.28±2.86 (p=0.08 vs Control, p=0.06 vs ControlPC)	1.77±0.25	1.75±0.32	1.70±0.26
TMT	Processing time, s	41.56±18.26 * # &	33.98±9.00 #	34.39±10.64	30.00±8.41
	Errors, mean±SD	0.12±0.33 ** &	0.43±0.62 &	0.33±59	0.63±0.68
SST	Total score	9.44±1.12	9.36±1.81	9.72±1.53	9.42±1.30

* Data are presented as mean±SD. Significant differences relative the Control group: * - p<0.05, ** - p<0.01, *** - p<0.001. Significant differences relative the ControlPC group: # - p<0.05, ### - p<0.001. & - p<0.05. Significant differences between the PCD and noPCD groups: && - p<0.01, &&& - p<0.001.

3.4. Associations between COVID-related parameters and neuropsychological testing

The results of linear regression analysis are shown in Table 5. Significant weak to moderate positive correlations between the number of post-COVID symptoms and HADS test results were found for the total sample of patients. Significant weak negative correlations were found for the number of post-COVID symptoms with immediate recall and total score in the WMT test for the total sample of patients. Significant moderate negative correlations between the WMT and COVID-related parameters were observed for the PCD patients: 1) the number of symptoms correlated with delayed recall and total score, 2) time after the recovery from the first COVID-19 correlated with immediate recall and assistance. The MoCA test showed only significant weak positive correlation between language score and the time after first recovery for the total sample and moderate negative correlation between orientation score and the time after the last recovery for the PCD group. The indexes of the TMT showed weak correlations with the time of the first recovery. The time of processing in the incongruent condition showed moderate positive correlation with the number of acute symptoms in the PCD patients.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 13 December 2023 doi:10.20944/preprints202312.0937.v1

Table 5. Correlations between COVID-related parameters and neuropsychological testing in patients with post COVID complications.

Test	Parameter	Number of COVID-19 episodes		Time after first COVID-19		Time after last COVID-19		Number of acute symptoms		Number of post-COVID symptoms	
	Sample	Total	PCD	Total	PCD	Total	PCD	Total	PCD	Total	PCD
HADS	Total score	-	-	-		-	-	-	-	0.36**	-
	Anxiety	-	-	-		-	-	-	-	0.41***	-
	Depression	-	-	-		-	-	-	-	0.27*	-
WMT	Total score	-	-	-		-	-	-	-	-0.27*	-0.39*
	Immediate recall	-	-	-	-0.49*	-	-	-	-	-0.24*	
	Immediate assistance	-	-	-	-0.61**	-	-	-	-	-	-
	Delayed recall	-	-	-	-	-		-	-	-	-0.42*
MoCA	Language	-	-	0.25*	-	-		-	-	-	-
	Orientation	-	-		-	-	-0.42*	-	-	-	-
TMT	Time	-	-	-0.24*	-	-	-	-		-	-
	Errors	-	-	-0.25*	-	-	-	-		-	-
SCWT	CW time	-	-	-	-	-	-	-	0.48*	-	-

Only the psychometric indexes for which significant correlations have been identified are presented.
Significance of Pearson's correlation coefficients: * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$.

4. Discussion

In our study, neurocognitive changes in patients diagnosed with depression as a complication of COVID-19 were assessed using objective psychometric tests. A key finding was that the PCD patients showed significantly worse results in several cognitive tests, specifically, decline in the MoCA, WMT and TMT, and near to significant decrease in the SCWT. In addition, insomnia index was higher in the PCD patients. This impairment of cognitive abilities in the PCD group was more prominent not only in comparison with two control groups (Control and ControlPC), but also in comparison with a large group of patients with post-COVID syndrome without diagnosed clinical depression (noPCD group). Additionally, we found significant correlations of the time after COVID-19 recovery with MoCA scores and TMT indexes, the number of post-COVID symptoms with WMT and HADS scores, and the number of acute symptoms with SCWT processing time.

Numerous studies reported cognitive impairment in the patients with MDD including deficits in executive function, processing speed, memory, and attention (reviewed by [14–17]). Global assessment of cognitive abilities using the MoCA test also shows impairment in the PCD patients [42–45]. About half of older patients with MDD scored below normal (25 scores or less) on the MoCA test [42,43], while a sample of patients with an age similar to our sample showed a lower percentage of cognitive decline [45]. Nyundo and Ismail [45] reported that 32.7% MDD patients have scores lower 26 (mean score was 26.56). Our results showed a similar mean score (26.48), but a smaller percentage (16%) of patients with scores less than 26. These differences might be likely explained by differences in the number of episodes and disease duration. In the study by Nyundo and Ismail [45], only 23% of patients had experienced 1-2 episodes and only in 8% of patients had disease duration less than a year. In our study, the number of episodes in all patients did not exceed 2 and in 56% of patients duration of the disease was less than a year. It should be noted that in our study, the decrease in the total score in the MoCA test was mainly associated with a decrease in memory (3.56 in patients with DMD vs 4.05 points in controls) and attention (5.44 in patients with DMD vs 5.84 points in controls) indices. These results were confirmed by a significant decrease in the WMT test and a downward trend in the Stroop test.

The majority of published studies reported memory deficits in the MDD patients manifested as immediate memory impairment. Xu et al. [46] found immediate visual memory impairment in

 doi:10.20944/preprints202312.0937.v1

patients in the depressed state and in remission compared to healthy controls. Shimizu et al. [47] reported both immediate and delayed verbal memory impairment in remitted MDD patients in comparison to healthy controls. Hammar et al. [46] also found that MDD patients show a deficit in immediate words recall compared to healthy controls. Baune [48] found differences only in the immediate but not in delayed memory. These findings are in accordance with our results showed impaired immediate verbal memory recall in the PCD patients compared to controls (total scores, immediate recall total score, immediate recall without assistance and with assistance) and the noPCD group (total scores, immediate recall total score). In contrast, Jia [49] showed that first episode drug-naïve depressive patients had deficits in delayed, but not in immediate memory. Hammar et al in the review article [15] suggested immediate memory impairment as an impaired informational encoding but not as a long-term memory deficit. Our results support this hypothesis. Based on our data, PCD patients showed similar results in immediate (9.04±1.40) and delayed (9.04±1.65) word recall while healthy controls indices were 9.21±1.18 and 9.83±0.48, correspondingly. Interestingly, in our study impairment in immediate word recall significantly correlated with the number of post-COVID symptoms for the total sample of patients, while for the sample of PCD patients the immediate word recall correlated with delayed recall. These differences might be explained by depression severity in PCD patients. Similar association between severity and delayed recall were shown in [15]. Large variability of delayed recall in patients with depression was observed (Table 4) in our study. At the same time, a significant negative correlation with immediate recall in PCD patients indicated a reduction of memory deficit over time after COVID-19.

Another distinctive feature of cognitive impairment in MDD is an impairment in executive function and processing speed detected by the TMT and Stroop task [14–17,50]. We also found a significant increase of processing speed with higher accuracy in the TMT in the PCD patients compared to controls. In the Stroop task, verbal fluency in the simple W condition and interference index in CW condition were worse (near significant) in the PCD patients compared to controls and noPCD group. According to literature, the impairment of executive function in MDD patients is linked to inhibition of automatic response in order to make a less automatic task-relevant response [15,51]. This explains the higher processing speed and lower number of errors in MDD patients that we observed. Moreover, several studies suggested that inhibition could be a trait marker in first-episode patients [15,51,52] that persisted in long-term follow up as was showed by Schmid and Hammar in 10-year longitudinal studies [15,52].

The results of the current study were similar to the published data reporting cognitive changes in MDD patients in objective cognitive tests. However, MDD etiology and PCD differed in the factors causing the specific condition. While MDD etiology is multifactorial [53], the cause of clinical depression in the PCD patients is COVID-19 infection. Despite the large evidence of cognitive and depressive post-COVID impairments [2–11,54], which persist after a year or more after recovery [9,55,56], we did not find the studies report the features of cognitive impairment in with clinically diagnosed post-COVID depression.

Several studies explored cognitive functions in relation to depressive symptoms. Poletti et al. [7] investigated cognitive function of COVID-19 survivors at 1, 3, and 6 months after recovery in comparison with healthy controls and MDD patients. The study showed that 75% of COVID-19 patients had impairment in at least one cognitive function. However, psychomotor coordination and processing speed in COVID-19 patients were worse than in healthy controls but better than in MDD patients. No difference between COVID-19 survivors and MDD patients was observed in verbal fluency and executive functions, but both groups showed lower results in those tests than healthy controls. No differences were found between COVID-19 patients and healthy controls in working memory and verbal memory. Pinnock et al. [57] in the prospective study of the post-COVID patients found reduction in processing speed in favor of execution accuracy, deficits in complex attention, memory, and mild to moderate depression and anxiety symptoms at 1.5 years after recovery. This is consistent with our results showing a decrease in processing speed in favor of accuracy in the TMT test, as well as memory deficits in the PCD patients.

 doi:10.20944/preprints202312.0937.v1

The study by Simonetti et al. [6] found association between post-COVID-19 syndrome and mixed depression, i.e., a specific sub-form of depression characterized by high level of excitatory symptoms. Unfortunately, this study did not examine cognitive impairment of PCD patients. Our results did not confirm prevalence of excitatory symptoms in post-COVID patients, in opposite, we found a longer processing time in the TMT and SCWT compared to controls.

According to the questionnaire, the PCD patients experienced significantly greater number of post-COVID symptoms, as well as more often suffer from anosmia, ageusia, insomnia, fatigue, attention and memory deficits, and panic attacks in comparison to the patients of the noPCD group, who also experienced post-COVID complications. These results are largely supported by objective test results documenting impairments in memory, executive function, and processing speed in post-COVID depression. The exception is the symptoms of anosmia (hyposmia). In contrast with other studies [20,58,59], we did not reveal any differences between post-COVID patients and controls in Sniffin's Stick Test. Overall, test results significantly correlated with the number of symptoms and recovery time.

Most researchers believe that neuroinflammation leaded to impaired connectivity might be the main cause of cognitive impairment after COVID-19. Several studies demonstrated neuroinflammation [60,61] as well as disrupted connectivity and demyelination [55,62–64] in post-COVID patients. Since microglial and astroglial reactivation lead to impaired oligodendrocyte functioning and renewal [65–67], demyelination or decreased remyelination also might play an important role in cognitive changes in PCD patients. The MRI study performed in the same group of PCD patients supported the hypothesis of brain demyelination after COVID-19 [68]. In that study, we used quantitative macromolecular proton fraction (MPF) mapping [69–71] that strongly correlated with myelin content [69,72–75]. The study showed more extensive brain demyelination in patients with post-COVID depression in comparison to controls and post-COVID patients without clinically diagnosed depression. Moreover, our study identified demyelination of inferior fronto-occipital fasciculus (IFOF) as the primary predictor of PCD presence and severity [68]. Anatomically, the IFOF connects early visual processing in the occipital lobe (cuneus and lingual gyri) and the parietal regions with frontal lobe regions [76,77] and also includes the connections between the cingulo-opercular and frontoparietal networks [77,78]. Therefore, the IFOF plays a critical role in semantic language processing, goal-oriented behavior, visual switching tasks, and executive function [76–78]. Based on these results, demyelination of the IFOF largely explains the results of psychological tests that we found in the current study: impairment of visual verbal processing, interference in the Stroop task, increased processing time in the serial connection test, immediate reproduction of words after reading them in patients with PCD.

There are still too few studies to confidently state that there are no specific cognitive impairments in patients with PCD. More research is needed to link post-COVID structural and functional brain changes with cognitive impairment and depression. Future directions including the MRI study of demyelination and connectivity, functional MRI, EEG studies in combination with neuropsychological testing could clarify the mechanisms underlying post-COVID syndrome.

5. Conclusions

The present study is the first to examine cognitive impairment in patients with clinically diagnosed post-COVID depression using neuropsychological testing. The PCD patients showed significantly less scores the MoCA test, decreased immediate memory recall in the WMT, decreased processing speed and higher accuracy in the TMT, worse (near significant) executive control and processing speed in the SCWT compared to controls and the patients with post-COVID complications without clinical depression. In addition, the number of post-COVID symptoms negatively correlated with immediate word memory recall and processing speed among all post-COVID patients. In PCD patients, negative correlations between number of post-COVID symptoms and delayed recall, time after recovery and immediate recall, and positive correlation between the number of acute symptoms and processing speed in the incongruent condition of the Stroop task were found. Taking into account

the results of our MRI study on the same sample of PCD patients, we believe that cognitive decline in these patients is, at least in part, related to extensive brain demyelination and, in particular, IFOF.

Author Contributions: Conceptualization, writing—original draft preparation, M.Kh.; Data curation, project administration, software M.S.; writing—review and editing, A.V.N.; investigation, D.K.; formal analysis, M.K.; formal analysis, V.P.; formal analysis, M.M.; investigation, V.O.; investigation, N.K.; investigation, A.L.; resources, Y.T, investigation, S.V.; investigation, E.S. All authors reviewed and approved the final version of the manuscript.

Funding: The study was funded by Russian Science Foundation (project No. 22-15-00481).

Institutional Review Board Statement: The study design was approved by the local Ethical Committee of the Mental Health Research Institute (№15/8.2022) and Bioethics Committee of Tomsk State University (№12/06.2022).

Data Availability Statement: Informed consent was obtained from all participants involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Soriano JB, Murthy S, Marshall JC, Relan P, D.J. Clinical Case Definition of Post-COVID-19 Condition by a Delphi Consensus. *Lancet Infect Dis* **2020**.
2. Ceban, F.; Ling, S.; Lui, L.M.W.; Lee, Y.; Gill, H.; Teopiz, K.M.; Rodrigues, N.B.; Subramaniapillai, M.; Di, J.D.; Cao, B.; et al. Fatigue and Cognitive Impairment in Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis. *Brain Behav. Immun.* **2020**, *101*, 93–135, doi:doi: 10.1016/j.bbi.2021.12.020.
3. Taquet, M.; Geddes, J.R.; Husain, M.; Luciano, S.; Harrison, P.J. 6-Month Neurological and Psychiatric Outcomes in 236 379 Survivors of COVID-19 : A Retrospective Cohort Study Using Electronic Health Records. *The Lancet Psychiatry* **2021**, *8*, 416–427, doi:10.1016/S2215-0366(21)00084-5.
4. Sobrino-Relaño, S.; Balboa-Bandeira, Y.; Peña, J.; Ibarretxe-Bilbao, N.; Zubiaurre-Elorza, L.; Ojeda, N. Neuropsychological Deficits in Patients with Persistent COVID-19 Symptoms: A Systematic Review and Meta-Analysis. *Sci. Rep.* **2023**, *13*, 1–14, doi:10.1038/s41598-023-37420-6.
5. Lauria, A.; Carfì, A.; Benvenuto, F.; Bramato, G.; Ciciarello, F.; Rocchi, S.; Rota, E.; Salerno, A.; Stella, L.; Tritto, M.; et al. Neuropsychological Measures of Post-COVID-19 Cognitive Status. *Front. Psychol.* **2023**, *14*, doi:10.3389/fpsyg.2023.1136667.
6. Simonetti, A.; Bernardi, E.; Margoni, S.; Catinari, A.; Restaino, A.; Ieritano, V.; Palazzetti, M.; Mastrantonio, F.; Janiri, D.; Tosato, M.; et al. Mixed Depression in the Post-COVID-19 Syndrome: Correlation between Excitatory Symptoms in Depression and Physical Burden after COVID-19. *Brain Sci.* **2023**, *13*, doi:10.3390/brainsci13040688.
7. Poletti, S.; Palladini, M.; Mazza, M.G.; De Lorenzo, R.; Irene, B.; Sara, B.; Beatrice, B.; Ceciclio, B.; Stefania, C.; Valentina, C.; et al. Long-Term Consequences of COVID-19 on Cognitive Functioning up to 6 Months after Discharge: Role of Depression and Impact on Quality of Life. *Eur. Arch. Psychiatry Clin. Neurosci.* **2022**, *272*, 773–782, doi:10.1007/s00406-021-01346-9.
8. Brown, L.A.; Ballentine, E.; Zhu, Y.; McGinley, E.L.; Pezzin, L.; Abramoff, B. The Unique Contribution of Depression to Cognitive Impairment in Post-Acute Sequelae of SARS-CoV-2 Infection. *Brain, Behav. Immun. - Heal.* **2022**, *22*, 100460, doi:10.1016/j.bbih.2022.100460.
9. Miskowiak, K.W.; Fugledalen, L.; Jespersen, A.E.; Sattler, S.M.; Podlekareva, D.; Rungby, J.; Porsberg, C.M.; Johnsen, S. Trajectory of Cognitive Impairments over 1 Year after COVID-19 Hospitalisation: Pattern, Severity, and Functional Implications. *Eur. Neuropsychopharmacol.* **2022**, *59*, 82–92, doi:10.1016/j.euroneuro.2022.04.004.
10. Cheetham, N.J.; Penfold, R.; Giunchiglia, V.; Bowyer, V.; Sudre, C.H.; Canas, L.S.; Deng, J.; Murray, B.; Kerfoot, E.; Antonelli, M.; et al. The Effects of COVID-19 on Cognitive Performance in a Community-Based Cohort: A COVID Symptom Study Biobank Prospective Cohort Study. *eClinicalMedicine* **2023**, *62*, 102086, doi:10.1016/j.eclinm.2023.102086.
11. Pistarini, C.; Fiabane, E.; Houdayer, E.; Vassallo, C.; Manera, M.R.; Alemanno, F. Cognitive and Emotional Disturbances Due to COVID-19: An Exploratory Study in the Rehabilitation Setting. *Front. Neurol.* **2021**, *12*, 1–8, doi:10.3389/fneur.2021.643646.

12. Ma, Y.; Li, W.; Deng, H.; Wang, L.; Wang, Y.; Wang, P. Prevalence of Depression and Its Association with Quality of Life in Clinically Stable Patients with COVID-19. **2020**.
13. Renaud-Charest, O.; Lui, L.M.W.; Eskander, S.; Ceban, F.; Ho, R.; Di Vincenzo, J.D.; Rosenblat, J.D.; Lee, Y.; Subramaniapillai, M.; McIntyre, R.S. Onset and Frequency of Depression in Post-COVID-19 Syndrome: A Systematic Review. *J. Psychiatr. Res.* **2021**, *144*, 129–137, doi:10.1016/j.jpsychires.2021.09.054.
14. Culpepper, L.; Lam, R.W.; McIntyre, R.S. Cognitive Impairment in Patients with Depression: Awareness, Assessment, and Management. *J. Clin. Psychiatry* **2017**, *78*, 1383–1394, doi:10.4088/JCP.tk16043ah5c.
15. Hammar, Å.; Ronold, E.H.; Rekkedal, G.Å. Cognitive Impairment and Neurocognitive Profiles in Major Depression—A Clinical Perspective. *Front. Psychiatry* **2022**, *13*, doi:10.3389/fpsyt.2022.764374.
16. Zuckerman, H.; Pan, Z.; Park, C.; Brietzke, E.; Musial, N.; Shariq, A.S.; Iacobucci, M.; Yim, S.J.; Lui, L.M.W.; Rong, C.; et al. Recognition and Treatment of Cognitive Dysfunction in Major Depressive Disorder. *Front. Psychiatry* **2018**, *9*, 1–11, doi:10.3389/fpsyt.2018.00655.
17. Wen, M.; Dong, Z.; Zhang, L.; Li, B.; Zhang, Y.; Li, K. Depression and Cognitive Impairment: Current Understanding of Its Neurobiology and Diagnosis. *Neuropsychiatr. Dis. Treat.* **2022**, *18*, 2783–2794, doi:10.2147/NDT.S383093.
18. Herman, B.; Bruni, A.; Zain, E.; Dzulhadj, A.; Oo, A.C.; Viwattanakulvanid Post-COVID Depression and Its Multiple Factors, Does Favipiravir Have a Protective Effect? A Longitudinal Study of Indonesia COVID-19 Patients. *PLoS One* **2022**, *17*, 1–20, doi:10.1371/journal.pone.0279184.
19. Pilotto, A.; Cristillo, V.; Cotti Piccinelli, S.; Zoppi, N.; Bonzi, G.; Sattin, D.; Schiavolin, S.; Raggi, A.; Canale, A.; Gipponi, S.; et al. Long-Term Neurological Manifestations of COVID-19: Prevalence and Predictive Factors. *Neurol. Sci.* **2021**, *42*, 4903–4907, doi:10.1007/s10072-021-05586-4.
20. Gözen, E.D.; Aliyeva, C.; Tevetoğlu, F.; Karaali, R.; Balkan, İ.İ.; Yener, H.M.; Özdoğan, H.A. Evaluation of Olfactory Function With Objective Tests in COVID-19-Positive Patients: A Cross-Sectional Study. *Ear, Nose Throat J.* **2021**, *100*, 169S-173S, doi:10.1177/0145561320975510.
21. Biederman, J.; Petty, C.R.; Fried, R.; Black, S.; Faneuil, A.; Doyle, A.E.; Seidman, L.J.; Faraone, S. V. Discordance between Psychometric Testing and Questionnaire-Based Definitions of Executive Function Deficits in Individuals with ADHD. *J. Atten. Disord.* **2008**, *12*, 92–102, doi:10.1177/1087054707305111.
22. Zigmond, A.S.; Snalth, R.P. The Hospital Anxiety and Depression Scale. Acta Psychiatr. Scand. [Revista En Internet] 2014 [Acceso 28 de Noviembre de 2019]; 64(5): 361-370. *Acta Psychiatr. Scand.* **1983**, *67*, 361–370.
23. Hamilton, M. A Rating Scale for Depression. *J. Neurol. Neurosurg. Psychiatry* **1960**, *23*, 56–62, doi:doi: 10.1136/jnnp.23.1.56.
24. Hamilton, M. Development of a Rating Scale for Depressive Illness. *Br. J. Soc. Clin. Psychol.* **1967**, *6*, 278–296, doi:DOI: 10.1111/j.2044-8260.1967.tb00530.x.
25. Chan Sui Ko, A.; Candellier, A.; Mercier, M.; Joseph, C.; Schmit, J.L.; Lanoix, J.P.; Andrejak, C. Number of Initial Symptoms Is More Related to Long COVID-19 than Acute Severity of Infection: A Prospective Cohort of Hospitalized Patients. *Int. J. Infect. Dis.* **2022**, *118*, 220–223, doi:10.1016/j.ijid.2022.03.006.
26. Fernández-de-las-Peñas, C.; Pellicer-Valero, O.J.; Navarro-Pardo, E.; Rodríguez-Jiménez, J.; Martín-Guerrero, J.D.; Cigarán-Méndezd, M. The Number of Symptoms at the Acute COVID-19 Phase Is Associated with Anxiety and Depressive Long-Term Post-COVID Symptoms: A Multicenter Study. *J. Psychosom. Res.* **2021**, *150*, 110625, doi:doi: 10.1016/j.jpsychores.2021.110625.
27. Durstenfeld, M.S.; Peluso, M.J.; Peyser, N.D.; Lin, F.; Knight, S.J.; Djibo, A.; Khatib, R.; Kitzman, H.; O'Brien, E.; Williams, N.; et al. Factors Associated with Long COVID Symptoms in an Online Cohort Study. *Open Forum Infect. Dis.* **2023**, *10*, 1–10, doi:10.1093/ofid/ofad047.
28. Asadi-Pooya, A.A.; Akbari, A.; Emami, A.; Lotfi, M.; Rostamihosseinkhani, M.; Nemati, H.; Barzegar, Z.; Kabiri, M.; Zeraatpisheh, Z.; Farjoud-Kouhanjani, M.; et al. Risk Factors Associated with Long Covid Syndrome: A Retrospective Study. *Iran. J. Med. Sci.* **2021**, *46*, 428–436, doi:10.30476/ijms.2021.92080.2326.
29. Nasreddine, Z.S.; Phillips, N.A.; Bedirian, V.; Charbonneau, S.; Whitehead, V.; Collin, I.; Cummings, J.L.; Chertkow, H. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J. Am. Geriatr. Soc.* **2005**, *53*, 695–699, doi:https://doi.org/10.1111/j.1532-5415.2005.53221.x.
30. Green, P.; Montijo, J.; Brockhaus, R. High Specificity of the Word Memory Test and Medical Symptom Validity Test in Groups with Severe Verbal Memory Impairment. *Appl. Neuropsychol.* **2011**, *18*, 86–94, doi:10.1080/09084282.2010.523389.

31. Allen, M.; Bigler, E.; Larsen, J.; Goodrich-Hunsaker, N.; Hopkins, R. Functional Neuroimaging Evidence for High Cognitive Effort on the Word Memory Test in the Absence of External Incentives. *Brain Inj.* **2007**, *21*, 1425–1428, doi:10.1080/02699050701769819.
32. Reitan, R.M. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept Mot Ski.* **1958**, *8*, 271–276.
33. Stroop, J.R. Studies of Interference in Serial Verbal Reactions. *J. Exp. Psychol.* **1935**, *18*, 643–662, doi:10.1037/h0054651.
34. Huang, C.L.-C. The Value of Patient-Administered Depression Rating Scale in Detecting Cognitive Deficits in Depressed Patients. *J. Clin. Med. Res.* **2010**, *2*, 27–33, doi:10.4021/jocmr2010.02.224w.
35. Freud, T.; Vostrikov, A.; Dwolatzky, T.; Punchik, B.; Press, Y. Validation of the Russian Version of the MoCA Test as a Cognitive Screening Instrument in Cognitively Asymptomatic Older Individuals and Those With Mild Cognitive Impairment. *Front. Med.* **2020**, *7*, 1–7, doi:10.3389/fmed.2020.00447.
36. Mahendran, R.; Chua, J.; Feng, L.; Kua, E.H.; Preedy, V.R. *The Mini-Mental State Examination and Other Neuropsychological Assessment Tools for Detecting Cognitive Decline*; Elsevier Inc., 2015; ISBN 9780124079397.
37. Hummel, T.; Konnerth, C.G.; Rosenheim, K.; Kobal, G. Screening of Olfactory Function with a Four-Minute Odor Identification Test: Reliability, Normative Data, and Investigations in Patients with Olfactory Loss. *Ann. Otol. Rhinol. Laryngol.* **2001**, *110*, 976–981, doi:10.1177/000348940111001015.
38. Rumeau, C.; Nguyen, D.T.; Jankowski, R. How to Assess Olfactory Performance with the Sniffin' Sticks Test®. *Eur. Ann. Otorhinolaryngol. Head Neck Dis.* **2016**, *133*, 203–206, doi:10.1016/j.anorl.2015.08.004.
39. Cousijn, J.; van Benthem, P.; van der Schee, E.; Spijkerman, R. Motivational and Control Mechanisms Underlying Adolescent Cannabis Use Disorders: A Prospective Study. *Dev. Cogn. Neurosci.* **2015**, *16*, 36–45, doi:10.1016/j.dcn.2015.04.001.
40. Tremblay, M.-P.; Potvin, O.; Belleville, S.; Bier, N.; Gagnon, L.; Blanchet, S.; Domingues, N.-S.; Gaudreau, G.; Macoir, J.; Hudon, C. The Victoria Stroop Test: Normative Data in Quebec-French Adults and Elderly. *Arch. Clin. Neuropsychol.* **2016**, *31*, acw029, doi:10.1093/arclin/acw029.
41. Bastien, C.H. Insomnia Severity Index. 28.
42. Blair, M.; Coleman, K.; Jesso, S.; Desbeaumes Jodoin, V.; Smolewska, K.; Warriner, E.; Finger, E.; Pasternak, S.H. Depressive Symptoms Negatively Impact Montreal Cognitive Assessment Performance: A Memory Clinic Experience. *Can. J. Neurol. Sci.* **2016**, *43*, 513–517, doi:10.1017/cjn.2015.399.
43. Wu, Z.; Su, G.; Lu, W.; Liu, L.; Zhou, Z.; Xie, B. Clinical Symptoms and Their Relationship with Cognitive Impairment in Elderly Patients with Depressive Disorder. *Front. Psychiatry* **2022**, *13*, doi:10.3389/fpsyt.2022.1009653.
44. Nyundo, A.A.; Ismail, A. The Influence of Major Depressive Disorders on Neurocognitive Function among Adults Living with HIV/AIDS in a Regional Referral Hospital in Dodoma, Tanzania. *Trop. Med. Int. Heal.* **2022**, *27*, 58–67, doi:10.1111/tmi.13699.
45. Ab Latiff, H.Z.; Ariaratnam, S.; Shuib, N.; Isa, M.R. Cognitive Decline and Its Associated Factors in Patients with Major Depressive Disorder. *Healthc.* **2023**, *11*, 1–11, doi:10.3390/healthcare11070950.
46. Xu, G.; Lin, K.; Rao, D.; Dang, Y.; Ouyang, H.; Guo, Y.; Ma, J.; Chen, J. Neuropsychological Performance in Bipolar I, Bipolar II and Unipolar Depression Patients: A Longitudinal, Naturalistic Study. *J. Affect. Disord.* **2012**, *136*, 328–339, doi:10.1016/j.jad.2011.11.029.
47. Shimizu, Y.; Kitagawa, N.; Mitsui, N.; Fujii, Y.; Toyomaki, A.; Hashimoto, N.; Kako, Y.; Tanaka, T.; Asakura, S.; Kusumi, I. Neurocognitive Impairments and Quality of Life in Unemployed Patients with Remitted Major Depressive Disorder. *Psychiatry Res.* **2013**, *210*, 913–918, doi:10.1016/j.psychres.2013.08.030.
48. Baune, B.T.; Miller, R.; McAfoose, J.; Johnson, M.; Quirk, F.; Mitchell, D. The Role of Cognitive Impairment in General Functioning in Major Depression. *Psychiatry Res.* **2010**, *176*, 183–189, doi:10.1016/j.psychres.2008.12.001.
49. Jia, Q.F.; Chen, P.; Zhu, H.L.; Chen, S.S.; Gu, X.C.; Yin, X.Y.; Wu, Y.H.; Yin, G.Z.; Hui, L. Cognitive Impairments in First-Episode Drug-Naïve Versus Medicated Depressive Patients: RBANS in a Chinese Population. *Psychiatr. Q.* **2019**, *90*, 471–480, doi:10.1007/s11126-019-09641-4.
50. Epp, A.M.; Dobson, K.S.; Dozois, D.J.A.; Frewen, P.A. A Systematic Meta-Analysis of the Stroop Task in Depression. *Clin. Psychol. Rev.* **2012**, *32*, 316–328, doi:10.1016/j.cpr.2012.02.005.
51. Miyake, A.; Friedman, N.P.; Emerson, M.J.; Witzki, A.H.; Howerter, A.; Wager, T.D. The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cogn. Psychol.* **2000**, *41*, 49–100, doi:10.1006/cogp.1999.0734.

52. Hammar, Å.; Isaksen, L.; Schmid, M.; Årdal, G.; Strand, M. Patients with Major Depression Show Intact Memory Performancegiven Optimal Conditions. *Appl. Neuropsychol.* **2011**, *18*, 191–196, doi:10.1080/09084282.2011.595445.
53. Li, Z.; Ruan, M.; Chen, J.; Fang, Y. Major Depressive Disorder: Advances in Neuroscience Research and Translational Applications. *Neurosci. Bull.* **2021**, *37*, 863–880, doi:10.1007/s12264-021-00638-3.
54. Ramani, C.; Davis, E.M.; Kim, J.S.; Provencio, J.J.; Enfield, K.B.; Kadl, A. Post-ICU COVID-19 Outcomes: A Case Series. *Chest* **2021**, *159*, 215–218, doi:10.1016/j.chest.2020.08.2056.
55. Huang, S.; Zhou, X.; Zhao, W.; Du, Y.; Yang, D.; Huang, Y.; Chen, Y.; Zhang, H.; Yang, G.; Liu, J.; et al. Dynamic White Matter Changes in Recovered COVID-19 Patients: A Two-Year Follow-up Study. *Theranostics* **2023**, *13*, 724–735, doi:10.7150/thno.79902.
56. Huang, Y.; Ling, Q.; Manyande, A.; Wu, D.; Xiang, B. Brain Imaging Changes in Patients Recovered From COVID-19: A Narrative Review. *Front. Neurosci.* **2022**, *16*, 1–12, doi:10.3389/fnins.2022.855868.
57. Pinnock, F.S.; Rich, J.B.; Vasquez, B.; Wiegand, M.; Patcai, J.; Troyer, A.K.; Murphy, K.J. Neurocognitive Outcome Following Recovery from Severe Acute Respiratory Syndrome - Coronavirus-1 (SARS-CoV-1). *J. Int. Neuropsychol. Soc.* **2022**, *28*, 891–901, doi:10.1017/S1355617721001107.
58. Vandersteen, C.; Payne, M.; Dumas, L.É.; Plonka, A.; D'Andréa, G.; Chirio, D.; Demonchy, É.; Risso, K.; Robert, P.; Fernandez, X.; et al. What about Using Sniffin' Sticks 12 Items Test to Screen Post-COVID-19 Olfactory Disorders? *Eur. Arch. Oto-Rhino-Laryngology* **2022**, *279*, 3477–3484, doi:10.1007/s00405-021-07148-y.
59. Bagnascoa, D.; Passalacquaa, G.; Braidoa, F.; Tagliabuea, E.; Cosinia, F.; Filaurob, M.; Ioppib, A.; Carobbiob, A.; Mocellinb, D.; Riccioa, A.M.; et al. Quick Olfactory Snif Fi n ' Sticks Test (Q-Sticks) for the Detection of Smell Disorders in COVID- 19 Patients. *World Allergy Organ. J.* **2021**, *14*, 100497, doi:http://doi.org/10.1016/j.waojou.2020.100497.
60. Braga, J.; Lepra, M.; Kish, S.J.; Rusjan, P.M.; Nasser, Z.; Verhoeff, N.; Vasdev, N.; Bagby, M.; Boileau, I.; Husain, M.I.; et al. Neuroinflammation after COVID-19 with Persistent Depressive and Cognitive Symptoms. *JAMA Psychiatry* **2023**, *80*, 787–795, doi:10.1001/jamapsychiatry.2023.1321.
61. Sriwastava, S.; Tandon, M.; Podury, S.; Prasad, A.; Wen, S.; Guthrie, G.; Kakara, M.; Jaiswal, S.; Subedi, R.; Elkhooly, M.; et al. COVID-19 and Neuroinflammation: A Literature Review of Relevant Neuroimaging and CSF Markers in Central Nervous System Inflammatory Disorders from SARS-COV2. *J. Neurol.* **2021**, *268*, 4448–4478, doi:10.1007/s00415-021-10611-9.
62. Huang, S.; Zhou, Z.; Yang, D.; Zhao, W.; Zeng, M.; Xie, X.; Du, Y.; Jiang, Y.; Zhou, X.; Yang, W.; et al. Persistent White Matter Changes in Recovered COVID-19 Patients at the 1-Year Follow-Up. *Brain* **2022**, *145*, 1830–1838, doi:10.1093/brain/awab435.
63. Qin, Y.; Wu, J.; Chen, T.; Li, J.; Zhang, G.; Wu, D.; Zhou, Y.; Zheng, N.; Cai, A.; Ning, Q.; et al. Long-Term Microstructure and Cerebral Blood Flow Changes in Patients Recovered from COVID-19 without Neurological Manifestations. *J. Clin. Invest.* **2021**, *131*, doi:10.1172/JCI147329.
64. Bispo, D.D. de C.; Brandão, P.R. de P.; Pereira, D.A.; Maluf, F.B.; Dias, B.A.; Paranhos, H.R.; von Glehn, F.; de Oliveira, A.C.P.; Regattieri, N.A.T.; Silva, L.S.; et al. Brain Microstructural Changes and Fatigue after COVID-19. *Front. Neurol.* **2022**, *13*, doi:10.3389/fneur.2022.1029302.
65. Butt, A.M.; Papanikolaou, M.; Rivera, A. Physiology of Oligodendroglia. In *Advances in Experimental Medicine and Biology*; 2019; Vol. 1175, pp. 117–128 ISBN 10.1007/9789811.
66. Bradl, M.; Lassmann, H. Oligodendrocytes: Biology and Pathology. *Acta Neuropathol.* **2010**, *119*, 37–53, doi:10.1007/s00401-009-0601-5.
67. Chapman, T.W.; Hill, R.A. Myelin Plasticity in Adulthood and Aging. *Neurosci. Lett.* **2020**, *715*, 134645, doi:10.1016/j.neulet.2019.134645.
68. Khodanovich, M.; Svetlik, M.; Kamaeva, D.; Usova, A.; Kudabaeva, M. Demyelination in Patients with Post-COVID Depression. *Biomedicines* **2023**, *Preprint*, 1–23, doi:10.20944/preprints202312.0698.v1.
69. Kisel, A.A.; Naumova, A. V.; Yarnykh, V.L. Macromolecular Proton Fraction as a Myelin Biomarker: Principles, Validation, and Applications. *Front. Neurosci.* **2022**, *16*, 1–10, doi:10.3389/fnins.2022.819912.
70. Yarnykh, V.L. Time-Efficient, High-Resolution, Whole Brain Three-Dimensional Macromolecular Proton Fraction Mapping. *Magn. Reson. Med.* **2016**, *75*, 2100–2106, doi:10.1002/mrm.25811.
71. Yarnykh, V.L. Fast Macromolecular Proton Fraction Mapping from a Single Off-Resonance Magnetization Transfer Measurement. *Magn. Reson. Med.* **2012**, *68*, 166–178, doi:10.1002/mrm.23224.

72. Khodanovich, M.Y.Y.; Sorokina, I.V.V.; Glazacheva, V.Y.Y.; Akulov, A.E.E.; Nemirovich-Danchenko, N.M.M.; Romashchenko, A.V. V.; Tolstikova, T.G.G.; Mustafina, L.R.R.; Yarnykh, V.L.L. Histological Validation of Fast Macromolecular Proton Fraction Mapping as a Quantitative Myelin Imaging Method in the Cuprizone Demyelination Model. *Sci. Rep.* **2017**, *7*, 1–12, doi:10.1038/srep46686.
73. Khodanovich, M.Y.; Pishchelko, A.O.; Glazacheva, V.Y.; Pan, E.S.; Akulov, A.E.; Svetlik, M.V.; Tyumentseva, Y.A.; Anan'ina, T.V.; Yarnykh Vasily Leonidovich Quantitative Imaging of White and Gray Matter Remyelination in the Cuprizone Demyelination Model Using the Macromolecular Proton Fraction. *Cells* **2019**, *8*, 1204, doi:10.3390/cells8101204.
74. Khodanovich, M.Y.; Gubskiy, I.L.; Kudabaeva, M.S.; Namestnikova, D.D.; Kisel, A.A.; Anan'ina, T. V.; Tumentceva, Y.A.; Mustafina, L.R.; Yarnykh, V.L. Long-Term Monitoring of Chronic Demyelination and Remyelination in a Rat Ischemic Stroke Model Using Macromolecular Proton Fraction Mapping. *J. Cereb. Blood Flow Metab.* **2021**, *41*, 2856–2869, doi:10.1177/0271678X211020860.
75. Khodanovich, M.Y.; Kisel, A.A.; Akulov, A.E.; Atochin, D.N.; Kudabaeva, M.S.; Glazacheva, V.Y.; Svetlik, M. V.; Medvednikova, Y.A.; Mustafina, L.R.; Yarnykh, V.L. Quantitative Assessment of Demyelination in Ischemic Stroke in Vivo Using Macromolecular Proton Fraction Mapping. *J. Cereb. Blood Flow Metab.* **2018**, *38*, 919–931, doi:10.1177/0271678X18755203.
76. Caverzasi, E.; Papinutto, N.; Amirbekian, B.; Berger, M.S.; Henry, R.G. Q-Ball of Inferior Fronto-Occipital Fasciculus and Beyond. *PLoS One* **2014**, *9*, doi:10.1371/journal.pone.0100274.
77. Conner, A.K.; Briggs, R.G.; Sali, G.; Rahimi, M.; Baker, C.M.; Burks, J.D.; Glenn, C.A.; Battiste, J.D.; Sughrue, M.E. A Connectomic Atlas of the Human Cerebrum-Chapter 13: Tractographic Description of the Inferior Fronto-Occipital Fasciculus. *Oper. Neurosurg.* **2018**, *15*, 5436–5443, doi:10.1093/ons/opy267.
78. Hausman, H.K.; Hardcastle, C.; Albizu, A.; Kraft, J.N.; Evangelista, N.D.; Boutzoukas, E.M.; Langer, K.; O'Shea, A.; Van Etten, E.J.; Bharadwaj, P.K.; et al. Cingulo-Opercular and Frontoparietal Control Network Connectivity and Executive Functioning in Older Adults. *GeroScience* **2022**, *44*, 847–866, doi:10.1007/s11357-021-00503-1.